IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: George H. Yoo	§	
	§	Group Art Unit: 1633
Serial No.: 10/747,798	§	
	§	Examiner: Priebe, Scott David
Filed: December 29, 2003	§	
	§	Atty. Dkt.: INRP:104US
For: p53 TREATMENT OF PAPILLOMAVIRUS AND CARCINOGEN-TRANSFORMED CELLS IN HYPERPLASTIC LESIONS	§	

CERTIFICATE OF ELECTRONIC SUBMISSION	
DATE OF FILING	December 18, 2006

APPELLANTS' REPLY TO EXAMINER'S ANSWER

PATENT

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Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants hereby submit this Reply Brief in response to the Examiner's Answer, dated October 26, 2006. It is believed that no fees are due in connection with this paper; however, should any fees be due the Commissioner is authorized to withdraw the appropriate fees from Fulbright & Jaworski Deposit Account No. 50-1212/INRP:104US.

STATEMENT OF THE CASE

This appeal presents the following issues:

1) Whether claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 are properly rejected under 35 U.S.C. §102(a) as being anticipated by Clayman, G. (Ref. C95 of the IDS filed August 16, 2004; "Clayman;"), as evidenced by Oda *et al.* (Carcinogenesis 17(9):2003-2008, 1996; "Oda") and Flaitz *et al.* (Oral Oncol. 34:448-453, 1998; "Flaitz"), and as evidenced by the minutes of the Recombinant DNA Advisory Committee ("RAC").

2) Whether claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 are anticipated under 35 U.S.C. §102(b) by the RAC, as evidenced by Oda and Flaitz.

3) Whether claims 1-14, 19-29, 38-50, and 55-60 are anticipated under 35 U.S.C. §102(b) by Nielsen *et al.* (U.S. Patent App. Pub. No. 2001/0044420; "Nielsen"), as evidenced by Oda and Flaitz.

4) Whether claims 1-15, 18-29, 33, 38-51, and 54-60 are anticipated by El-Deiry (WO 99/66946) under 35 U.S.C. §102(b).

5) Whether claims 16, 17, 31, 32, 52, and 53 are properly rejected under 35 U.S.C. §103(a) as being unpatentable over either (i) RAC as evidenced by Oda and Flaitz, as applied to above, or (ii) El-Deiry further in view of Zhang *et al.* (WO 00/29024; "Zhang").

Appellants set forth the following response to the Examiner's Answer. Appellants will rely on the response set forth in their Appeal Brief to any issues not specifically addressed herein.

A. Clayman, as Evidenced by Oda, Flaitz, and RAC, Fails to Anticipate Claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 35 U.S.C. §102(a)

1. Clayman Does Not Expressly or Inherently Disclose Papillomavirus-Transformed Cells

As detailed in the appeal brief (see section VII. A, pages 5-9), Clayman does not anticipate the claims because it fails to expressly or inherently describe each limitation of the claimed invention. As acknowledged by the Examiner, Clayman does not state or disclose that each of the premalignancies or cancers being treated include cells infected with HPV. See Office Action dated April 14, 2006. Further, Oda and Flaitz teach that a substantial fraction of patients with oral and cervical cancer ***do not*** have HPV infected cells. Thus, because Clayman fails to expressly or inherently teach or suggest each limitation of the claimed invention, there can be no anticipation.

The Examiner argues that because a certain percentage of patients in Oda and Flaitz have HPV-infected tumor cells, that there must be inherent anticipation. However, the Examiner misinterprets the case law pertaining to inherent anticipation. Inherent anticipation arises when "the prior art necessarily functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1946 (Fed. Cir. 1999). While it may be possible that an oral or cervical premalignancy or cancer may have HPV infected cells, this is not sufficient to establish inherent anticipation. See *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365, 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) ("[I]nherency ... ***may not be established by probabilities or possibilities***. Inherent anticipation would require that ***every*** oral and cervical cancer ***necessarily include*** HPV infected cells. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.") (emphasis added).

Oda and Flaitz establish that there is the possibility that a patient with an oral or cervical premalignancy or cancer may have HPV infected cells. By the same token, Oda and Flaitz also establish that there is the possibility that a patient with an oral or cervical premalignancy or cancer may ***not*** have HPV infected cells. Thus, contrary to the Examiner's assertion, Oda and Flaitz do not establish that "half or most of such patients would necessarily be made up of HPV infected cells."

The Examiner asserts that "if the PTO were to grant a patent to these claims, Appellant could bar those of skill in the art from practicing the cited prior art methods on half or most of the patients for which the methods were designed and developed." Appellants disagree. First, it is noted that this is not a proper standard for determining whether a prior art reference anticipates. In order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. See *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1432 (Fed. Cir. 1997). As set forth above, there is no anticipation because the cited prior art reference (Clayman) fails to expressly or inherently disclose an HPV infected cell. The Examiner has failed to set forth substantial evidence that the prior art methods are necessarily directed to the treatment of papillomavirus transformed cells.

The present invention is not directed to obtaining patent protection of a method of inhibiting the growth of cells that are not infected with HPV. Granting patent protection of the pending claims would not allow Appellant to exclude the public from practicing the prior art method of inhibiting the growth of cells that are not infected with HPV. *See Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1379, 67 USPQ2d 1664 (Fed. Cir. 2003), citing *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1346, 51 USPQ2d 1943, 1945 (Fed. Cir. 1999)

("[I]f granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated. That the claimed method might be applied in the treatment of cells not infected by HPV is not relevant to the issue of whether Clayman anticipates the claimed invention.

2. *Clayman Does Not Expressly or Inherently Disclose Limitations of Dependent Claims 4, 6, 18, 33, and 54*

a) "a keratinocyte"

Clayman does not expressly or inherently disclose the limitation "wherein said cell is a keratinocyte" in claim 4. Appellant identifies no disclosure in Clayman pertaining to any malignancy or premalignancy involving keratinocytes. The patients set forth in Clayman have preneoplastic lesions of the oral cavity. Most of the oral cavity is lined by nonkeratinized squamous epithelium, and not keratinocytes.

The Examiner incorrectly cites Flaitz (page 452, col. 1) as teaching that squamous cells are keratinocytes. While Flaitz teaches that keratinocytes are a type of squamous cell ("terminally differentiated squamous cells"), it does not teach that all squamous cells are keratinocytes. Because squamous cells are not necessarily keratinocytes, there is no inherent anticipation.

b) "a skin cell" (claim 6)

Clayman does not expressly or inherently disclose treatment of "a skin cell," as set forth in claim 6. Rather, Clayman pertains to treatment of oral cavity, which is lined by mucosa and not skin. Therefore, Clayman additionally fails to anticipate dependent claim 6.

The Examiner argues that the claim term "skin" should be given a "broadest reasonable meaning," and that mucosa of the mouth and cervix are considered to be a type of skin. In support of his assertion, he cites several sources from the world wide web.

The Examiner has not applied the proper standard in construing the term "skin." In the absence of an express intent to impart a novel meaning to the claim terms, the words are presumed to take on the ordinary and customary meanings attributed to them by those of ordinary skill in the art." *MPEP* 2111.01, citing *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298, 67 USPQ2d 11132, 1136 (Fed. Cir. 2003). Further, the ordinary customary meaning of terms are evidenced by a variety of sources, including the written description and claims. See *MPEP* 2111.01, citing, *e.g.*, *DeMarini Sports, Inc., v. Worth, Inc.*, 239 F.3d 1314, 1324, 57 USPQ2d 1889, 1894 (Fed. Cir. 2001). No novel meaning to the term "skin" was imparted in the specification. The ordinary and customary meaning of the term "skin" does not include mucosal tissue, such as mucosa of the mouth and cervix. As evidence of the ordinary and customary meaning of the term "skin," Appellant cites to originally filed claim 6 (which recites "wherein said cell is a skin cell") and originally filed claim 7 (which recites "wherein said cell is a mucosal cell"). The fact that both claims depends from claim 1 supports an ordinary meaning whereby skin is distinct from mucosa. Had Appellants meant to interpret skin to include mucosa (i.e., the meaning construed by the Examiner), then Appellant would have made claim 7 dependent upon claim 6. Further, the following sections of the specification support a plain and ordinary meaning of skin to distinct from mucosa (e.g., cervical or oral mucosa):

- Page 3, lines 25-26: "The cell can be a keratinocyte, an epithelial cell, a skin cell, a mucosal cell, or any other cell that can undergo transformation by a papillomavirus."
- Page 9, lines 4-6: "Human papillomaviruses characterized to date are associated with lesions confined to the epithelial layers of skin, or oral, pharyngeal, respiratory, and anogenital mucosae."
- Page 16, lines 7-9: "Similarly, where the cell is an epithelial cell, skin cell, mucosal cell or any other cell that can undergo transformation by a papillomavirus, the promoter used in the embodiment will be one which has activity in that particular cell type. Page 16, lines 7-9.
- Page 35, line 25 – page 36, line 5: "…lesions of the skin of the face and neck…"
- Page 37, lines 26-27: "The lesion include, but is not limited to, cells such as keratinocytes, epithelial cells, skin cells, and mucosal cells. 37, line 26-27."

In each of the above cited sections of the specification

c) a "douche solution" (claims 18, 33, and 54) or "a liquid carrier formulated for vaginal delivery" (claim 33)

As to claims 18 and 33, Clayman additionally does not anticipate because it does not expressly or inherently disclose "a douche solution" (claims 18 and 33) or "a liquid carrier formulated for vaginal delivery" (claim 33). The Examiner has argued that a douche is simply a jet of liquid. Appellant notes that there is no disclosure in Clayman pertaining to any jet of liquid applied to any part of the body, vagina or otherwise.

The Examiner argues that Clayman and RAC teach formulations formulated as douche solutions. However, neither reference includes any disclosure pertaining to douche solutions or

liquid carriers formulated for vaginal delivery. Both Clayman and RAC teach "oral rinses" (see, *e.g.*, Exhibit 4 of appeal brief, page 11, first full paragraph). There is no disclosure in either reference pertaining to formulations for vaginal delivery, nor is there any indication in either references that any formulation set forth therein can be formulated as a douche solution or for vaginal delivery.

In view of foregoing, it is respectfully submitted that Clayman fails to expressly or inherently anticipate the claimed invention. Therefore, it is respectfully requested that the Board reverse the rejection under 35 U.S.C. §102(a) based on Clayman.

B. RAC, as Evidenced by Oda and Flaitz, Fails to Anticipate Claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 Under 35 U.S.C. §102(b)

As is the case with Clayman (discussed *supra*), RAC does not anticipate the claims because it fails to expressly or inherently describe each limitation of the claimed invention. The Examiner admits that RAC does not disclose papilloma virus infection in cells in the lesion, and thus concedes that there is no express anticipation. He argues that this characteristic is inherent in view of Oda and Flaitz., and that one of ordinary skill in the art of oral cancer would have been aware that treatment of hyperplastic lesions as described in RAC would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells. However, as with the previous rejection, the Examiner has applied an incorrect legal standard in setting forth a rejection based on inherent anticipation. The discussion above pertaining to absence of inherent anticipation is incorporated into this section. Because RAC fails to inherently anticipate the claimed invention, it is respectfully requested that the Board reverse the rejection under 35 U.S.C. §102(b) based on RAC.

C. Nielsen, as Evidenced by Oda and Flaitz, Fails to Anticipate Claims 1-14, 19-29, 38-50, and 55-60 Under 35 U.S.C. §102(b)

As with Clayman and RAC, the Examiner's interpretation of inherent anticipation with respect to Nielsen is incorrect. The discussion above regarding why Clayman and RAC do not inherently anticipate the claims is herein incorporated into this section. As discussed above, ***occasional results are not inherent***. Without an inherent teaching regarding HPV-transformed cells in Nielsen, there can be no anticipation.

D. El-Deiry Fails to Anticipate Claims 1-15, 18-29, 33, 38-51, and 54-60 Under 35 U.S.C. §102(b)

El-Deiry does not anticipate the claimed invention because it does not expressly or inherently disclose administration of a polynucleotide encoding a p53 polypeptide to a papillomavirus-transformed cell. The Examiner argues that the recitation of "p73" in El-Diery is sufficient to anticipate the claims because p73 is a homologue of p53.

However, "p73" is not a "homologue" of p53, as the term "homologue" is defined in Applicants' specification. Applicants' specification recite: "Throughout this application, the term 'p53' is intended to refer to the exemplified p53 molecules as well as all p53 homologues from other species." Specification, page 14, lines 5-6. The "exemplified p53" referred to in this context is human p53. One of ordinary skill in the art would understand this to be the case because the section of the application where this definition appears addresses in detail the role of p53 in ***human*** cancer. See page 12, line 23 –page 14, line 21. Indeed the application is replete with reference to p53, its role in human cancer, and the role of ***human*** papillomavirus in human cancer. See, *e.g*, page 10, line 1 – page 14, line 21. One of ordinary skill in the art would understand that if the exemplified p53 molecule was a human p53, then in the context of the present specification, "all p53 homologues from other species" refers to p53 molecules from

species other than human p53. Thus, the ordinary artisan would understand that "p53" as used in the present specification refers to human p53 and p53 molecules from other species.

When an application contains a definition for a claim term, the defined meaning of that term controls over the plain meaning of the term, and the claims must be examined using that meaning assigned by the specification. *MPEP* 2111.01.III and 2173.05(a). The Examiner has presented his own definition of "orthologue," "homologue," and "paralogue," without setting forth any definition from a text or source. Appellant, without concurring that the definitions set forth by the Examiner are in accordance with any plain meaning, nevertheless note that the defined meaning set forth in the specification controls, and that Appellant is not confined to definitions used in the prior art. *Id.*

El-Diery contains no disclosure pertaining to administration of human p53 to any papillomavirus-transformed cell. Nor does El-Diery disclose any p53 molecule from another species (*i.e.*, from a species other than human, such as a mouse p53). The Examiner, by not setting forth any argument, appears to concede this point.

As evidence to support that a person of ordinary skill in the art would understand the definition of "p53" set forth in the instant specification, Appellant has submitted the Declaration of Louis Zumstein, PhD. See Exhibit 8 of appeal brief. Dr. Zumstein, a person of skill in the art with over 13 years of experience in the biotechnology field, has read the above definition of "p53" in the specification and has declared that:

> "[a]s a scientist in the biotechnology field, I feel that the aforementioned lines regarding p53 indicate that this passage is specific for human p53 and p53 in other species. I do not believe from reading this passage that "p53" as used in this passage would refer to proteins other than p53 that might share some functional characteristics with p53. Furthermore, as a scientist in the biotechnology field, it is my belief that p73 is not a homologue of p53."

Exhibit 8 of appeal brief, paragraphs 5-6.

Further, Dr. Zumstein bases his opinion on specific differences between p53 and p73. For example, in contrast to p53 deficient mice, those mice lacking p73 showed no increased susceptibility to spontaneous tumorigenesis. Exhibit 8 of appeal brief, paragraph 6. Further, he notes that unlike p53, p73 is not activated by DNA damage. *Id.* In view of the foregoing, "p73" is not a "homologue," as defined by the specification.

Further, regarding dependent claims, El-Deiry additionally does not anticipate claims 4, 6, 18, 33, and 54 because it does not expressly or inherently disclose "a keratinocyte," (claim 4), "a skin cell" (claim 6), a "douche solution" (claims 18, 33, and 54), or "a liquid carrier formulated for vaginal delivery" (claim 33). The reasons are as discussed above.

E. Claims 16, 17, 31, 32, 52, and 53 Are Not Properly Rejected Under 35 U.S.C. §103(a) as Being Unpatentable Over Either (i) RAC as evidenced by Oda and Flaitz, as applied to above, or (ii) El-Deiry Further in View of Zhang

The Examiner has not met the PTO's burden of establishing a *prima facie* case of obviousness because he has not shown that the cited combination of references teach or suggest each limitation of the claimed invention. For the reasons set forth above, RAC fails to teach or suggest any lesion that includes papillomavirus-transformed cells, and El-Deiry fails to teach or suggest a polynucleotide encoding a p53. Further, El-Deiry provides no disclosure pertaining to topical application of any polynucleotide to papillomavirus-transformed cells. Zhang *et al.* fails to remedy the deficiency of RAC and El-Deiry because it is only cited as teaching a flavorant.

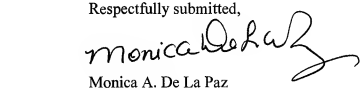
Further, the Examiner has failed to establish a *prima facie* case of obviousness because he has not set forth any suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teaches. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991). No

such teaching or suggestion has been set forth by the Examiner. The Examiner cites RAC and El Deiry as describing delivery of liquid comprising an adenoviral vector to the mouth, and Zhang as teaching a flavorant in a pharmaceutical composition. However, the claims at issue are directed to inhibiting, suppressing or preventing growth of papillomavirus-transformed cells in a hyperplastic lesion. No specific motivation to provide for inhibiting, suppressing or preventing growth of a papillomavirus-transformed cells in a hyperplastic lesion using a flavorant-containing composition containing p53. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Because no such suggestion has been cited by the Examiner, there can be no *prima facie* case of obviousness.

CONCLUSION

It is respectfully submitted, in light of the above, none of the pending claims are properly rejected. Therefore, Appellants request that the Board reverse the pending grounds for rejection.

Respectfully submitted,



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